REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 1-14 are pending in this application, of which claims 5, 6, 13, and 14 are under active consideration.

2. Patentability Remarks

a. 35 U.S.C. § 103(a)

On pages 3-10 of the Office Action, the Examiner rejects claims 5, 6, 13, and 14 as allegedly being unpatentable over Urbanek *et al.* (Journal of Medicinal Chemistry, 2001;44(11):1777-93)("Urbanek" hereafter) in view of U.S. Patent No. 7,008,411 ("Mandrusov" hereafter). The Examiner asserts that Urbanek discloses a genus of 9,10-phenanthrenediones that reads on the compounds of the instant claims, and that one of the compounds taught by Urbanek has only an extra CH_2 linker separating the O atom from the phenyl ring in comparison to the compound of instant claim 13. The Examiner also asserts that the compounds of Urbanek selectively inhibit CD45, which is a "family of transmembrane protein tyrosine phosphatases (PTPs) that are expressed ***exclusively by hematopoietic cells***." Instant Office Action at page 4, line 4 (emphasis added).

The Examiner asserts that Urbanek teaches that, "CD45 plays a critical role in T-cell receptor (TCR)-mediated signaling." Instant Office Action at line 1. Additionally, the Examiner asserts that according to Urbanek, current therapies targeted at reducing immune-cell activation in conditions such as organ transplant rejection and autoimmune diseases also affect cells ***outside the immune system*** and thus may be toxic. The Examiner further asserts that Urbanek discloses that immunosuppressants such as cyclosporine and FK506 can cause toxicities and malignancies, and that the effects of the immunosuppressant rapamycin are ***not limited to cells of the immune system***, and can affect endothelial cells and smooth muscle cells. According the Examiner, Urbanek also discloses that the 9,10-phenanthrenediones CD45 inhibitors of Urbanek are ***more selective*** agents than other anti-proliferative agents like rapamycin. The Examiner admits that Urbanek does not teach treating damage to normal tissue attributable to heart disease, or the compound of instant claim 13.

Additionally, the Examiner asserts that Mandrusov discloses a method for treating coronary artery and related diseases such as atherosclerotic occlusions and vulnerable plaque by using a drug

eluting stent. The Examiner further asserts that Mandrusov teaches examples of the drugs that can be loaded onto the stent, including "rapamycin, …, antiproliferative substances, antineoplastic agents, …, alpha-interferon, …, and dexamethasone." Instant Office Action at page 6, line 10.

The Examiner contends it would have been obvious to one of ordinary skill in the art to combine the teachings of Urbanek and Mandrusov to treat a patient with coronary heart disease with the stent of Mandrusov loaded with a compound disclosed by Urbanek to control atherosclerotic occlusions and vulnerable plaques. The Examiner reasons that Mandrusov suggests that agents including rapamycin and antiproliferative substances can be used to treat coronary artery diseases, and that Urbanek discloses that 9,10-phenanthrenedione compounds have antiproliferative activity that is selective for CD45 and are more selective than rapamycin. The Examiner also asserts that it would have been obvious to arrive at the compounds of the instant claims because one of skill would have expected that compounds with similar structures have similar activities, and therefore would have had sufficient motivation and expectation of success to modify the compounds of Urbanek to make the compounds of the instant claims. The Examiner thus concludes that the instant claims are obvious over Urbanek in view of Mandrusov. Applicant respectfully disagrees.

The basis for the Examiner's rejection is that there was some teaching, suggestion or motivation to combine Urbanek with Mandrusov to arrive at the claimed invention. *See* MPEP § 2143.G. Under this reasoning, the claimed invention is obvious only if (a) there was some teaching, suggestion, or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the cited references; and (b) there was reasonable expectation of success. MPEP § 2143.G. Applicant submits that one of ordinary skill in the art would have had no motivation to arrive at the claimed subject matter by combining the teachings of Urbanek and Mandrusov.

The Examiner's rejection is predicated on the existence of a link between (i) Mandrusov's alleged teaching that rapamycin and antiproliferative drugs can be used to treat coronary artery diseases by being loaded onto a drug-eluting stent; and (ii) Urbanek's teaching that 9,10-phenanthrenediones have antiproliferative activity that is similar to, but more selective than rapamycin. Applicant submits that the Examiner presents a highly-selective reading of the scope of what Mandrusov teaches. Furthermore, while the Examiner acknowledges Urbanek's teaching of higher selectivity of 9,10-phenanthrenediones as compared to rapamycin, the Examiner misconstrues the significance of this disclosure. As explained further below, rather than making it

more desirable to use 9,10-phenanthrenediones together with Mandrusov's stent, the higher selectivity makes it ***less desirable***.

Mandrusov discloses a drug eluting stent. *See, e.g.*, Mandrusov at column 4, line 28. The drug is intended to stabilize a vulnerable plaque. *See, e.g.*, Mandrusov at column 1, line 6 *and* column 4, line 60 *and* column 12, line 32. As to which agents can be loaded onto the stent, Mandrusov teaches that, "[r]epresentative therapeutic or biologically active agents include, but are ***not limited to***, ***proteins*** such as vascular endothelial growth factor (VEGF) in any of its multiple isoforms, fibroblast growth factors, monocyte chemoatractant protein 1 (MCP-1), transforming growth factor alpha (TGF-alpha), transforming growth factor beta (TGF-beta) in any of its multiple isoforms,… ***genes*** encoding these proteins, ***cells*** transfected with these genes, ***pro-angiogenic peptides*** such as PR39 and PR11, and pro-angiogenic ***small molecules*** such as nicotine." Mandrusov at column 4, line 62 (emphasis added). Moreover, Mandrusov teaches that stents can be loaded with, "lipid lowering agents, antioxidants, extracellular matrix synthesis promoters, inhibitors of plaque inflammation and extracellular degradation, estradiol drug classes and its derivatives," Mandrusov at column 5, line 14, cytokines and growth factors, Mandrusov at column 7, line 41, and anti-inflammatory agents. Mandrusov at column 12, line 34.

This massive genus of possible agents for use in Mandrusov's stent stands in stark contrast to the Examiner's selective assertion that the drugs that can be loaded onto the stent include, "rapamycin, …, antiproliferative substances, antineoplastic agents, …, alpha-interferon, …, and dexamethasone." Instant Office Action at page 6, line 10. In fact, the passage from which the Examiner quotes actually encompasses the following

> Examples of therapeutic or biologically active agents include but are not limited to rapamycin, actinomycin D (ActD) and their derivatives, antiproliferative substances, antineoplatic, antinflammatory, antiplatelet, anticoagulant, antifebrin, antithrombin, antimitotic, antibiotic and antioxidant substances. Examples of antineoplastics include taxol (paclitaxel and docetaxel). Examples of antiplatelets, anticoagulants, antifibrins and antithrombins include sodium heparin, low molecular weight heparin, hirudin, Ilb/IIIa platelet membrane receptor antagonist and recombinant hirudin. Examples of antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluororacil, adriamycin and mutamycin. Examples of cytostatic or antiproliferative agents include angiopeptin, calcium channel blockers (such as Nifedipine), Lovastatin (an inhibitor of HMG-CoA reductase, a cholestrol lowering drug from Merck). Other therapeutic or biologically active

> agents which may be utilized include alpha-interferon, genetically engineered epithelial cells and dexamethasone

Mandrusov at column 12, line 64. In essence, Mandrusov teaches that ***any*** drug known in the art that ***might*** have some positive effect on plaque stabilization can be used. This reads on a laundry list of countless drugs. Mandrusov gives no direction as to whether any of these agents actually work in treating vulnerable plaques, how any of the agents actually work in stabilizing vulnerable plaques, or whether any of these agents is particularly desirable. Mandrusov does not provide a single working example that would point one of skill to any particular agent among the thousands of possibilities.

Furthermore, nowhere does Mandrusov ever hint at a link between agents that are used to treat autoimmune disorders and organ graft rejection—like 9,10-phenananthrenediones are, as taught by Urbanek—and treating atherosclerotic occlusions and vulnerable plaques. The Examiner is correct that Mandrusov teaches using anti-proliferative agents like rapamycin in a stent, and that 9,10-phenanthrenediones also have anti-proliferative effects. But even if one of skill were to choose to use rapamycin in the stent taught by Mandrusov, among all the thousands of possibilities, the cell-specificity of the anti-proliferative effects of drugs like rapamycin and 9,10-phenanthrenediones is different. For example, as the Examiner acknowledges, Urbanek teaches that, "the anti-proliferative effects of rapamycin… ***are not limited to cells of the immune system***, and can affect growth factor-induced proliferation of fibroblasts, endothelial cells, hepatocytes, and ***smooth muscle cells***." Instant Office Action at page 5, line 12 (emphasis added). Urbanek teaches that these effects on cells ***outside*** the immune system are ***undesirable***, but it is the anti-proliferative effects of rapamycin on ***smooth muscle cells*** that makes this drug desirable for use in the stent taught by Mandrusov. In other words, at the time Mandrusov was filed, there was a known link between the effects of rapamycin and plaque stabilization that provided the proper motivation to use this drug in a stent.

It was known at the time of filing that drug-eluting stents could be loaded with anti-proliferation drugs like paclitaxel and rapamycin in order to improve outcomes after stent deployment. *See* Patterson *et al.* (Arterioscler Thromb Vasc Biol, 2006;26:1473-80)("Patterson" hereafter) at page 1473, column 2, line 3. Mandrusov discloses that both of these drugs can be loaded onto a stent. Mandrusov at column 12, line 65 *and* column 13, line 3. Patterson discloses that, "[b]oth of these drugs have been shown to ***inhibit smooth muscle migration and proliferation*** in vitro…" Patterson at page 1473, column 2, line 11. Patterson also discloses that

rapamycin acts through FK506-binding protein 12 to inhibit activation of the regulatory mTOR, thereby inhibiting cell proliferation in ***smooth muscle cells***. Patterson at page 1474, column 1, line 15. The use of rapamycin in stents makes sense because stents are used to stabilize vulnerable plaques in blood vessels, and blood vessels are made from smooth muscle. Accordingly, one of skill based on medical knowledge at the time of filing, might have selected to use rapamycin in Mandrusov's stent because of the anti-proliferative effects of rapamycin on smooth muscle—not simply because it generically had anti-proliferative effects.

To have any motivation to use a particular drug, such as rapamycin, there must be some rational basis for selecting the drug; the mechanism of action of the drug, or the specificity of the drug must make sense. The Examiner has failed to present any evidence of a connection between the mechanism of action or cell-specificity of 9,10-phenanthrenedione of Urbanek and unstable plaques. Urbanek teaches that 9,10-phenanthrenediones selectively inhibit CD45 and thereby specifically inhibit ***T-cell proliferation***. Urbanek at abstract *and* page 1788, column 1, line 13. Urbanek suggests that 9,10-phenanthrenediones are superior to drugs like cyclosporine, FK506, and rapamycin because these latter drugs have affects ***outside the immune system***, and therefore produce undesirable side-effects when used to treat ***autoimmune disorders*** and ***organ graft rejection***. Urbanek teaches that immunosuppressive drugs—like 9,10-phenanthrenediones—"that more specifically target the signaling pathways ***in the hematopoietic cells*** responsible for initiating and maintain inflammation should have fewer and/or different side effects than cyclosporine, FK506, or rapamycin." Urbanek at page 1777, column 1, line 30 (emphasis added). This is why Urbanek focuses specifically on the use of 9,10-phenanthrenediones for treating autoimmune disorders and organ graft rejection. *See* Urbanek at abstract.

The Examiner admits that Urbanek fails to teach that there is any use for the 9,10-phenanthrenediones in treating heart disease. *See* Instant Office Action at page 5, line 18 ("Urbanek et al. do not teach the instant claimed method for treating damage to normal tissue attributable to heart disease…"), and neither Urbanek nor Mandrusov establish any link between T-cell proliferation and either atherosclerotic occlusions or vulnerable plaques. The mere fact that Mandrusov teaches that—among the thousands of agents it discloses—some drugs like rapamycin which generically have anti-proliferative effects, and the fact that 9,10-phenanthrenediones also have anti-proliferative effects is not evidence that one of ordinary skill in the art would have any motivation to use just any anti-proliferative drug in Mandrusov's stent. Without any link between T-cell proliferation and plaque instability, one of skill would not have had any motivation to use a drug

that is touted as a superior drug for treating ***autoimmune disorders*** and ***organ graft rejection***. That is why the instantly claimed subject matter is not obvious—Applicant had the insight that the compounds of the instant claims could be used to treat damage to normal tissue attributable to heart disease, not because of antiproliferative activity but because of their effect on promoting cell survival, migration, and proangiogenesis. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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